This Month in Genetics

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Let's Start at the Very Beginning

You really can't tackle a problem until you understand its root cause. When that problem is cancer, physicians typically classify disease according to the cells or tissues affected; in fact, however, there might be several different underlying causes in each class. Besides this, some cancers don't fall neatly into a class, leaving an orphan group for which the underlying mechanisms are likely to be disparate and difficult to uncover. This approach to classifying cancer complicates treatment and means it is not unlikely that a patient will receive a therapy to which their cancer will not respond. Realizing that this is less than ideal, Maxson et al. looked with a molecular lens at two hard-to-classify cancers—chronic neutrophilic leukemia (CNL) and atypical chronic myeloid leukemia (CML)–to see whether they could do better. They performed deep sequencing of the cancers and limited their search for relevant mutations to a set of genes related to cellular signaling. More than half of the samples they sequenced had mutations in one of these, *CSF3R*, which encodes a receptor for colony-stimulating factor. In vitro experiments indicate that the mutations fall into two classes that lead to different downstream-signaling consequences that, in turn, make cells harboring these mutations susceptible to different inhibitors. This background work served as the impetus for treating a CNL patient with a drug that was selected on the basis of the *CSF3R* mutation found in his cancer. The treatment reduced the patient's white cell and neutrophil counts and normalized the platelet counts. Maybe starting at the beginning—with the mutation that contributes to the cancer—will be a fruitful way to group cancers and to tackle this disease.

Maxson et al. (2013). N. Engl. J. Med. 368, 1781–1789.

As if the *FMR1*-Related Disorders Weren't Complicated Enough…

Fragile X syndrome is the classic example of trinucleotide repeat expansion that leads to a null mutation. If the CGG repeat in the 5′ region of *FMR1* expands beyond a certain size, methylation of the region transcriptionally silences the gene, and the lack of expression of the encoded protein leads to neurodevelopmental issues. A little over 10 years ago, it was noticed that people with a premutation-sized CGG repeat at this locus suffered from tremors and ataxia, and this was first attributed to a toxic RNA. Todd et al. pondered the fact that this RNA toxicity doesn't jive with the observation that neuronal inclusions from people with this disorder appear to be protein mediated. Via experiments in flies, mice, cell cultures, and people, they demonstrate that CGG premutations are translated, through a non-AUG-initiated mechanism, into polyglycine- and polyalanine-containing products that are found in the neuronal inclusions. Evidence in *Drosophila* suggests that this repeat-associated non-AUG (RAN) translation contributes to neuronal toxicity. If you're keeping track, that means no protein, too much RNA, and aberrant translation at this locus all seem to contribute various disease phenotypes associated with *FMR1* repeat expansion.

Todd et al. (2013). Neuron 78, 440–455.

Inhibitors of Altered IDH1 and IDH2 Induce Cellular Differentiation

Two unexpected culprits in several cancer types, including glioma, acute myeloid leukemia (AML), and sarcoma, are IDH1 and IDH2, enzymes that normally convert isocitrate to α-ketoglutarate. The cancer-associated alterations reside in the catalytic pockets of IDH1 and IDH2 and confer them with a novel activity that produces the *R*-enantiomer of 2-hydroxyglutarate (*R*-2HG). This product accumulates in tumors and competitively inhibits α-ketoglutarate-dependent dioxygenases, which in turn alters epigenetic patterns and promotes malignancy. Because these changes confer a nonnative function, the altered enzymes are plausible candidates for cancer therapy, particularly because there are recurrent mutations in certain cancers. Wang et al. and Rohle et al. each identified an inhibitor of one of these cancer-associated enzymes. Both inhibitors reduce production of *R*-2HG and induce differentiation in cells containing the relevant alteration. Beyond potential therapeutic applications, these inhibitors implicate altered IDH1 and IDH2 in the maintenance of cancer, not just as initial drivers of a tumor.

Wang et al. (2013). Science 340, 622–626.
Rohle et al. (2013). Science 340, 626–630.

Using the Rare to Understand the Common

Several large genome-wide association studies have implicated a number of genomic regions in body mass index (BMI). Despite these successes, only a very minor fraction of the variance in BMI can be explained by common SNPs. Wheeler et al. figured that if they started with a sample from the extreme end of BMI, they might uncover

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http://dx.doi.org/10.1016/j.ajhg.2013.05.017.

something new. In their severe early-onset obesity (SCOOP) sample, they looked for association between obesity and SNPs or copy-number variants (CNVs) across the genome. Although some loci that they pulled out, such as *FTO* and *MC4R*, were not surprises, they also found novel associations with obesity. Single, rare CNVs were in excess in the SCOOP sample, and an ingenuity pathway analysis of the genes disrupted by the CNV highlighted G-protein-coupled receptors. These more rare and extreme cases of obesity thus provide new targets for investigation of the ways in which we all regulate our BMI.

Wheeler et al. (2013). Nat. Genet. 45, 513–517.

Screening for All, Some, or Few

Only a minority of colon cancers are due to Lynch syndrome, but its implications for the patient and for the family are substantial, in terms of both the recommended screening and treatment strategies. Several different published guidelines exist for the identification of at-risk families. In general, the guidelines aim to maximize the detection of affected families but in the most cost-effective manner. Because some truly affected families won't meet these guidelines and because other families might just fall through the cracks, some groups—such as the Evaluation of Genetic Applications in Practice and Prevention (EGAPP) and the National Society of Genetic Counselors—advocate universal Lynch syndrome screening in patients newly diagnosed with colon cancer. To get a sense of how well the family-history-based risk assessments are used, Cross et al. collected information on >1,000 cases of metastatic colon cancer via seven institutions in the Cancer Research Network. They found that even when the relevant risk information is collected, it is rarely used. In this sample, Lynch syndrome screening was performed for 3% of individuals, which is only a minority of those whose health records indicate that they meet screening guidelines. Beyond these cases with documented indication of Lynch syndrome risk, there were a number of other families for whom complete risk analysis could not be performed. Despite the fact that family-history information was collected in 80% of cases overall, it often lacked essential detail for use in risk assessment, such as the age of onset of cancers in the family. Because of the shortcomings in the application of screening guidelines, this group of authors recommends universal screening for Lynch syndrome so that fewer affected families will be missed.

Cross et al. (2013). Genet. Med. Published online May 2, 2013. http://dx.doi.org/10.1038/gim.2013.43.

This Month in Our Sister Journals

Hey, Are We Related?

Identifying segments of identity by descent (IBD) has a number of applications for genome analysis, including phasing data and detecting evidence of natural selection, but it is computationally intensive to look for these segments in population data sets. Browning and Browning describe a new method for IBD-segment detection, Refined IBD, and explore its performance on real and simulated SNP and sequence data. This two-stage approach is efficient and accurate and produces haplotype-phase output that can be useful for certain downstream analyses.

Browning and Browning. (2013). Genetics 194, 459–471.